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RISK OF CANCER IN WOMEN RECEIVING HORMONE REPLACEMENT THERAPY

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Cancer risk following treatment with non-contraceptive estrogens was studied in a population-based cohort of 23,244 women. Complete follow-up for an average of 6.7 years revealed 1,087 incident cancers *versus* 962.5 expected (relative risk/RR/ = 1.13; 95% confidence interval 1.10–1.20). We confirmed the recent findings of a more detailed analysis of the same cohort, based on a 1-year shorter follow-up period, namely: a markedly increased risk of endometrial cancer (RR = 1.8; 1.5–2.1), notably in women receiving potent estrogens, *i.e.*, conjugated estrogens or estradiol (RR = 2.0; 1.6–2.4), and a slightly increased risk of breast cancer (RR = 1.1; 1.0–1.2). A slightly decreased risk of invasive cervical cancer (RR = 0.8; 0.5–1.2) is most likely due to more frequent smear taking than in the background population. There was no increase in the risk of cancer of ovary (RR = 1.0; 0.8–1.2), pancreas (RR = 0.8; 0.5–1.2), large bowel (RR = 1.0; 0.8–1.2) or kidney (RR = 1.0; 0.7–1.4). The risk of developing cancer in liver or biliary tract was lower than expected (RR = 0.4; 0.2–0.7), particularly in women who had used potent estrogens (RR = 0.3; 0.1–0.6), an unexpected finding which warrants further studies. Increased risks of malignant melanoma (RR = 1.5; 1.0–2.1) and lung cancer (RR = 1.3; 0.9–1.7) need cautious interpretation because of their low magnitude, the absence of a biological gradient when subgroups were analyzed and the slightly higher prevalence of smokers in the cohort than in the background population.

Hormone replacement therapy in women in the peri- and post-menopausal periods is not only an effective remedy for symptoms related to hormone deficiency such as hot flushes, night sweats and vaginal dryness. In view of the many established or conceivable hormonal actions in different organs, delivery of potent estrogens might also improve our understanding of hormonal effects. The best established of these effects of estrogen replacement therapy are the increased risk of developing endometrial cancer (Ziehl, 1982; Brinton, 1984) and the protective effect against osteoporotic fractures (Cummings *et al.*, 1985). There is also accumulating evidence to support the view that the incidence of breast cancer increases after long-term treatment (Brinton, 1984; Bergkvist *et al.*, 1989) and that such treatment may prevent ischemic heart disease (Bush and Barrett-Connor, 1985) and rheumatoid arthritis (Vandenbroucke *et al.*, 1986).

Apart from these various effects on health, the etiological role of estrogens in cancer at other sites needs clarification. Associations have been suggested between exogenous estrogens and cancer of the ovary (Brinton, 1984; Smith *et al.*, 1984; Hartge *et al.*, 1988; Weiss *et al.*, 1982; Cramer *et al.*, 1983), uterine cervix (Brinton, 1986; Vessey, 1986), liver (Falk, 1982; Bosch and Munos, 1988; Conter and Longmire, 1988), and malignant melanoma (Brinton, 1984; Holman *et al.*, 1984); hormone receptor-like proteins have been found in pancreatic (Benz *et al.*, 1986), colorectal (Sica *et al.*, 1984) and renal cancers (Vugrin, 1987) and in meningiomas (Glick *et al.*, 1983; Moguilewsky *et al.*, 1984) and malignant melanomas (Fisher *et al.*, 1979; Chaudhuri *et al.*, 1980). Hormonal mechanisms have been suggested for large-bowel cancer (Schottenfeld and Winawer, 1982; Weiss *et al.*, 1981) and estrogens are known to induce renal cancer in certain animals (Kirkman and Bacon, 1950; Liehr *et al.*, 1986).

Two prospective epidemiological studies have addressed some of these observations (Hunt *et al.*, 1987; Pettiti *et al.*, 1987). Both are based on small numbers of observed cases—56 cancers at all sites (Hunt *et al.*, 1987) and 109 deaths from all causes (Pettiti *et al.*, 1987), respectively—and are focused on female reproductive cancers. In the present study we had the opportunity of analyzing more than 1,000 cancers that occurred in a large population-based cohort of women who had received hormone replacement therapy.

SUBJECTS AND METHODS

The cohort

All women who had been prescribed replacement estrogens for climacteric conditions were identified through prescription forms for estrogens supplied from all the pharmacies in the Uppsala health care region, comprising about 1.2 million inhabitants. The period of recruitment started in April 1977 and ended in March 1980. The national registration number, which permits exclusive identification of any person living in Sweden, and data on the brand, dose and package size and the date of purchase were computerized from these forms. The final cohort was based on 77,147 prescription forms which were estimated to correspond to at least 92% of all women who had received such prescriptions in the region during the period of investigation. The forms corresponded to 23,244 women aged 35 years or more living in the health care region and having had at least one prescription. The mean age at entry was 54.5 years. The procedures have been described by Persson *et al.* (1983*a*).

On the basis of the prescription recordings, all women in the cohort were grouped in 3 different ways: (1) years of follow-up were calculated from the date of the first recorded prescription (date of entry into the cohort) until the end of the observation period as defined below. (2) Two different categories, based on the compounds, were defined. One comprised all women registered as having had at least one prescription of any of the potent estrogenic compounds, namely conjugated estrogens (CE; 0.625 mg or 1.25 mg) or estradiol (E2, mainly estradiol valerate 1–2 mg and to a lesser extent ethinyl estradiol 8–10 μg). The other category comprised those who had received other estrogens only: estriol compounds (1–2 mg)—biologically weak estrogens used mainly for treatment of urogenital atrophic lesions—accounted for most of the prescriptions in this group. The mean age at entry was lower in the former (52.6 years) than in the latter (59.9 years) group of women. (3) In order to roughly separate women treated for postmenopausal vasomotor symptoms (hot flushes, night sweats) from those with symptoms related to genito-urinary atrophy, the age at the time of the first-recorded prescription was used to identify those who were younger and older than 60 years when included in the cohort.

Characterization of the cohort

The sub-cohort. In order to characterize the women in the total cohort more fully with respect to hormone exposure and

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potential confounding factors, a 1/30 random sample of 735 women was chosen and a questionnaire was issued to all of them in 1980; this was answered satisfactorily by 653 (89%). The questionnaire provided detailed information on various personal characteristics, exposure to estrogens before and after the period of prescription recording, intake compliance and the use of cyclically added progestagens. In order to facilitate recall, a list of all existing estrogen and progestagen preparations in Sweden was presented (Persson *et al.*, 1983*b*). In 1982 and 1984, additional questionnaires were sent to the women in the subcohort who had answered the initial one in order to ascertain their exposure after 1980.

According to the questionnaires, 9% of the women reported no intake and 50% had started their treatment before the period of the prescription recording in April 1977. Estradiol compounds accounted for 56% of all treatment periods, conjugated estrogens for 22% and other types of estrogens (mainly estriol compounds) for 22%. In 31% of the treatment periods, progestagens had been added for 7–10 days per treatment cycle. The median duration of treatment by the end of 1983 was 3.7 years.

Population sample. The cohort was also characterized with the aim of finding out to what extent external comparisons with the cancer incidence in the general population might be confounded by a different distribution of risk factors for various malignant diseases. For each woman in the sub-cohort described above, controls were selected randomly from the entire background population in the Uppsala health care region by the use of Swedish population registries. Matching was done for sex and age. A questionnaire, similar to that used for characterization of the sub-cohort, was mailed to all women in the population sample. Satisfactorily answered questionnaires were returned by 1,039 (78.1%). The distribution of various potential confounding factors is shown in Table I. Apart from a slightly higher proportion of current smokers and a higher educational level in the sub-cohort, no substantial difference was revealed between the groups. However, the prevalence figures for prior hysterectomy and bilateral oophorectomy were higher in the cohort than in the general population.

Follow-up

Complete follow-up of the cohort was achieved for an observation period up to the end of 1984, through register linkages by means of the national registration number. The nationwide Registry of Causes of Death was used to determine dates of death, and the National Cancer Registry (1987) to identify all incident cases of malignant diseases that were diagnosed in the cohort.

TABLE I – DISTRIBUTION OF VARIOUS POSSIBLE CONFOUNDING FACTORS IN THE COHORT OF WOMEN WHO RECEIVED ESTROGEN REPLACEMENT THERAPY—REPRESENTED BY THE SUB-COHORT SAMPLE—AND IN AN AGE-MATCHED SAMPLE FROM THE GENERAL POPULATION

Variable	Sub-cohort N = 653	Population sample N = 1,039
Smoking		
Never smokers	64.6%	68.8%
Ex-smokers	8.7%	10.1%
Current smokers[2]	26.8%	20.1%
Height (cm) mean[1]	163.7	162.8
Weight (kg) mean	66.5	66.1
Age at menarche (years) mean	13.6	13.6
Age at menopause (years) median[4]	50	51
Nulliparity	12.7%	12.9%
Hysterectomy[3]	19.0%	10.6%
Oophorectomy[3]	10.7%	4.1%
Level of daily physical activity		
High	4.7%	4.5%
Moderate	23.7%	21.5%
Low	50.2%	52.0%
Sedentary	21.4%	21.9%

[1]$p < 0.05$.–[2]$p < 0.01$.–[3]$p < 0.001$.–[4]Estimated by life-table technique.

Analyses

The total number of person-years at risk for the women in the cohort was calculated from the date of the first recorded prescription to death or to the end of follow-up on December 31, 1984. For specific cancer sites, the person-year calculations were censored at the date of diagnosis for this particular site. The total expected number of cases was calculated from the person-years and the age-specific incidence rates per calendar year and 5-year age group in the region from which the cohort was recruited. The rate ratio was then calculated as the ratio of the observed to the expected number of cases with its 95% confidence interval, based on the Poisson distribution of the observed number of cases.

RESULTS

Overall results

At the end of the follow-up period on December 31, 1984, a total of 1,087 cancers had occurred in the entire cohort, as against 962.47 expected, yielding a relative risk (RR) of 1.13 with a 95% confidence interval of 1.06–1.20. There was no evidence of a trend in overall cancer incidence in relation to the number of years of follow-up; the relative risk was 1.16 during the first 5 years and 1.05 during subsequent years. Nor was the overall risk of developing cancer higher in women who had been prescribed potent estrogens (RR = 1.14) than in those who had used mainly estriol (RR = 1.11). Likewise, similar relative risks were found for women who entered the cohort before the age of 60 (RR = 1.15) and at older ages (RR = 1.09).

The total numbers of observed and expected cases are shown by site in Table II. Apart from the analyses by site based on a selection of sites made in advance, *a posteriori* analyses were performed for each of the major sites accounting for the "remainder" (Table III). Some sites were associated with an unexpectedly high relative risk which departed significantly from unity, namely the vulva/vagina, the skin other than malignant melanoma, and connective tissue (Table III).

Reproductive organs

Ovarian cancer. The observed number of ovarian cancers (64) was close to the expected one of 66.6. Further analyses of duration of follow-up, estrogenic compound and age at the start of follow-up disclosed no pattern of risk differentials or trends (Table IV). In this analysis, the number of person-years at risk—and consequently the expected number of cases—was slightly overrated on account of an approximately 6% higher prevalence of oophorectomies in the cohort than in the background population (Table I). Adjustment for this difference would yield an increase in the overall relative risk from 0.96 to about 1.0.

Cervical cancer. Overall, the number of observed cases of invasive cervical cancer was only slightly lower than that expected, with a relative risk of 0.79 (Table II). Adjustment for the higher prevalence of hysterectomy than in the background population (Table I) yielded an overall relative risk of about 0.9. There was evidence of a lower risk in women receiving potent estrogens (RR = 0.6; 0.3–1.0) than in those receiving less potent compounds and in those younger than 60 years at the start of follow-up (RR = 0.6; 0.4–1.0) than in those aged over 60 (Table V). Confounding by compound might have biased the latter risk estimate. Stratified analysis revealed,

TABLE II – OVERALL RELATIVE RISK (RR) WITH 95% CONFIDENCE INTERVAL (CI) OF DEVELOPING VARIOUS MALIGNANT DISEASES AFTER NON-CONTRACEPTIVE ESTROGEN TREATMENT

Site	ICD-7 code	Observed number	Expected number	RR	95% CI
Ovary	175	64	66.64	0.96	0.74–1.23
Uterine cervix	171	27	34.05	0.79	0.52–1.15
Endometrium	172	139	78.01	1.78	1.50–2.10
Breast	170	300	270.24	1.11	0.99–1.24
Biliary tract and liver, primary	155	13	31.69	0.41	0.22–0.70
Pancreas	157	24	30.92	0.78	0.50–1.15
Colon and rectum	153–154	98	102.91	0.95	0.77–1.16
CNS	193	27	32.97	0.82	0.54–1.19
Lung	162–163	46	36.45	1.26	0.92–1.68
Kidney	180	34	32.37	1.05	0.73–1.47
Malignant melanoma	190	31	21.36	1.45	0.99–2.06
Remainder		284	274.30	1.04	0.92–1.16
All sites		1,087	962.47	1.13	1.10–1.20

TABLE III – OVERALL RELATIVE RISK OF DEVELOPING CANCER AT SOME SITES NOT SELECTED IN ADVANCE FOR ANALYSIS

Site	ICD-7 code	Observed number	Expected number	RR	95% CI
Vulva/vagina	176	16	6.8	2.3	1.3–3.8
Bladder	181	26	17.2	1.5	1.0–2.2
Other malignant neoplasms of skin	191	35	13.6	2.6	1.8–3.6
Thyroid	194	15	13.3	1.1	0.6–1.9
Other endocrine glands	195	31	28.9	1.1	0.7–1.5
Connective tissue	197	10	4.7	2.1	1.0–3.9
Other, unspecified	199	32	32.0	1.0	0.7–1.4
Lymphosarcoma, reticulosarcoma	200	21	21.2	1.0	0.6–1.5
Mycosis fungoides	205	9	8.8	1.0	0.5–2.0

TABLE IV – RELATIVE RISK OF DEVELOPING OVARIAN CANCER AFTER ESTROGEN TREATMENT

Category	Observed number	Expected number	RR	95% CI
Overall	64	66.6	0.96	0.74–1.23
Years of follow-up				
0–1	21	20.0	1.1	0.7–1.6
2–3	20	18.8	1.1	0.7–1.6
4–5	14	18.3	0.8	0.4–1.3
>6	9	9.5	0.9	0.4–1.8
Compound[1]				
CE and/or E2	45	48.3	0.9	0.7–1.3
Other	19	18.4	1.0	0.6–1.6
Age at start of follow-up, years				
<50	14	12.0	1.2	0.6–2.0
50–59	31	38.7	0.8	0.5–1.1
≥60	19	15.9	1.2	0.7–1.9

[1]CE = conjugated estrogens; E2 = estradiol; other = mainly estriol.

however, the same pattern in relation to potent and less potent compounds (Table V).

Endometrial cancer. The overall relative risk for invasive endometrial cancer was 1.78 (Table II), and when the high prevalence of prior hysterectomy (Table I) was taken into account this figure was 2.0. The risk was less pronounced after treatment with less potent estrogens (RR = 1.2; 95% CI 0.8–1.8) than after treatment with potent ones (RR = 2.0; 95% CI 1.6–2.4). These findings are in agreement with data in a more detailed analysis based on a 1-year shorter follow-up period (Persson *et al.*, 1989).

Breast cancer. The slightly increased risk of breast cancer (Table II) and the risk differential between other estrogens (RR = 1.0; 95% CI 0.8–1.3) and estradiol or conjugated estrogens (RR = 1.1; 95% CI 1.0–1.3) are also in accordance with recent data based on follow-up through 1983 (Bergkvist *et al.*, 1989).

Gastrointestinal cancers

Biliary tract and primary liver cancer. The risk of developing cancer in the liver or biliary tract was significantly lower than expected (RR = 0.41; 95% CI 0.22–0.70). There was no trend with increasing duration of follow-up after entry into the cohort. A markedly lower relative risk was found, however, for women who had received conjugated estrogens or estradiol (RR = 0.3) or were younger than 60 years (RR = 0.2), than in those who used less potent compounds (RR = 0.6) or were 60 years of age or older (RR = 0.6), respectively (Table VI).

Pancreatic cancer. The observed number of cases of pancreatic cancer was slightly and non-significantly lower than the expected value (RR = 0.76) (Table II). The decreased risk was virtually confined to those who received potent (RR = 0.6; 95% CI 0.3–1.1) rather than other estrogens (RR = 1.1; 95% CI 0.6–1.8). No clear pattern was seen in relation to the duration of follow-up or age at inclusion in the cohort.

Colorectal cancer. There was no evidence of an overall association between estrogen use and cancer of the large bowel (RR = 0.95; Table II). Neither did separate analyses by site reveal any heterogeneity, although a non-significantly decreased relative risk of 0.8 was found for the left colon (Table

TABLE V – RELATIVE RISK OF DEVELOPING INVASIVE CERVICAL CANCER AFTER ESTROGEN TREATMENT

Category	Observed number	Expected number	RR	95% CI
Overall	27	34.1	0.8	0.5–1.2
Years of follow-up				
0–4	22	25.2	0.9	0.6–1.3
>5	5	8.9	0.6	0.2–1.3
Compound[1]				
CE and/or E2	15	24.9	0.6	0.3–1.0
Other	12	9.2	1.3	0.7–2.3
Age at start of follow-up				
<60	17	26.0	0.6	0.4–1.0
≥60	10	8.0	1.2	0.6–2.3
Compound stratified by age				
<60, CE and/or E2	12	21.4	0.6	0.3–1.0
Other	5	4.7	1.1	0.4–2.5
≥60, CE and/or E2	3	3.5	0.9	0.2–2.5
Other	7	4.5	1.5	0.6–3.2

[1]CE = conjugated estrogens; E2 = estradiol; other = mainly estriol.

TABLE VI – RELATIVE RISK OF DEVELOPING PRIMARY CANCER IN THE LIVER AND BILIARY TRACT AFTER ESTROGEN TREATMENT

Category	Observed number	Expected number	RR	95% CI
Overall	13	31.7	0.4	0.2–0.7
Years of follow-up				
0–4	8	21.7	0.4	0.2–0.7
>5	5	10.0	0.5	0.2–1.2
Compound[1]				
CE and/or E2	5	18.9	0.3	0.1–0.6
Other	8	12.8	0.6	0.3–1.2
Age at start of follow-up, years				
<60	4	17.0	0.2	0.1–0.6
≥60	9	14.7	0.6	0.3–1.2

[1]CE = conjugated estrogens; E2 = estradiol; other = mainly estriol.

VII). Colonic and rectal cancer were therefore grouped in the further analyses and there was no relative risk which differed significantly from unity in any of the subgroups defined by years of follow-up, compound or age at entry into the cohort (Table VII).

Other cancers

CNS tumors. A slight deficit was found in the number of tumors occurring in the central nervous system (Table II). The (non-significantly) decreased relative risk was confined to women who received potent estrogens (RR = 0.7; 0.4–1.2) and were younger than 60 years at entry into the cohort (RR = 0.7; 0.4–1.2). No trend was observed in relation to the number of years of follow-up. The risk estimates were not materially altered when the analysis was confined to brain tumors alone; the observed number of cases was the same (Kirkman and Bacon, 1950), whereas the expected number was slightly reduced (30.5) in relation to all CNS tumors.

Lung cancer. There was a slight excess (RR = 1.26) in the observed number of lung cancers. The risk estimates for the first 5 years of follow-up were similar to those during subsequent ones. Treatment with potent (CE, E2) and other estrogens also entailed approximately the same relative risk (1.2 *vs.* 1.3). Most of the excess number of cases occurred in women who were under (RR = 1.3) rather than over (RR = 1.1) 60 years of age at entry into the cohort. Restriction of the analysis to the more specified disease entities trachea, bronchus and lung, primary (with ICD-7 codes 162.0 and 162.1) resulted in almost identical risk estimates.

Renal cancer. The numbers of cases observed and expected were in close agreement (Table II). Subgroup analyses by years of follow-up, compound and age at entry further supported the conclusion that there was no association between exogenous estrogens and the occurrence of renal cancer.

Malignant melanoma. The relative risk of developing malignant melanoma was increased to 1.45 (Table II). This increase was seemingly confined to women younger than 60 at entry into the cohort (RR = 1.7). Nevertheless, subgrouping by compound yielded a lower risk estimate for women who had received potent estrogens (RR = 1.3) than for those treated mainly with estriol (RR = 1.9) (Table VIII).

DISCUSSION

Before discussing the various and generally reassuring findings in this cohort study, some of its strengths and limitations have to be considered. The population-based nature of the cohort, the complete follow-up with respect to survival and cancer incidence, the completeness of the National Cancer Registry (1987) and the use of expected incidence rates in the same geographical area should minimize or eliminate several potential sources of bias. The relatively large number of observed cases made the overall estimates of relative risk fairly stable for most of the cancer sites and types.

Several different shortcomings need to be specially emphasized, however. First, since complete individual exposure data were available only for a 1/30 sample (the sub-cohort), subgrouping by compound, years of follow-up and age at the start of observation was based solely on prescription recordings during the 3-year period 1977 through 1980. This will necessarily entail a substantial misclassification based on estrogen use before and after this period of time. Thus, a certain proportion of the women to whom only "other estrogens"—mainly estriol—were prescribed may have received the more potent drugs before 1977. Also, some of the women who were older than 60 years on inclusion in the cohort started their exposure before this age, whereas the younger age group should have been defined adequately. From the fact that about 50% of the cohort women were currently receiving treatment at the start of the prescription recording (Persson *et al.*, 1983*b*), it follows that misclassification by years of follow-up will tend to conceal any

TABLE VII – RELATIVE RISK OF DEVELOPING COLORECTAL CANCER AFTER ESTROGEN TREATMENT

Category	Observed number	Expected number	RR	95% CI
Overall	98	102.9	1.0	0.8–1.2
Site				
All colon	62	67.1	0.9	0.7–1.2
Right colon[1]	30	31.3	1.0	0.7–1.4
Left colon[2]	20	25.4	0.8	0.5–1.2
Rectum	36	35.8	1.0	0.7–1.4
Years of follow-up				
0–4	70	70.0	1.0	0.8–1.3
>5	28	33.0	0.9	0.6–1.2
Compound[3]				
CE and/or E2	60	65.7	0.9	0.7–1.2
Other	38	37.2	1.0	0.7–1.4
Age at start of follow-up, years				
<60	61	61.7	1.0	0.8–0.3
≥60	37	41.2	0.9	0.6–1.2

[1]Includes ICD-7 codes 153.0 (ascending) and 153.1 (transverse including flexures).–[2]Includes ICD-7 codes 153.2 (descending) and 153.3 (sigmoid).–[3]CE = conjugated estrogens; E2 = estradiol; other = mainly estriol.

TABLE VIII – RELATIVE RISK OF DEVELOPING MALIGNANT MELANOMA AFTER ESTROGEN TREATMENT

Category	Observed number	Expected number	RR	95% CI
Overall	31	21.4	1.45	0.99–2.06
Years of follow-up				
0–4	22	15.6	1.4	0.9–2.1
>5	9	5.8	1.5	0.7–3.0
Compound[1]				
CE and/or E2	20	15.7	1.3	0.8–2.0
Other	11	5.7	1.9	1.0–3.5
Age at start of follow-up, years				
<60	28	16.7	1.7	1.1–2.4
≥60	3	4.7	0.6	0.1–1.9
Compound stratified by age				
<60, CE and/or E2	20	13.8	1.4	0.9–2.2
other	8	2.9	2.8	1.2–5.5
≥60, CE and/or E2	0	1.9	0	
other	3	2.8	1.1	0.2–3.1

[1]CE = conjugated estrogens; E2 = estradiol; other = mainly estriol.

trend in the relative risk in relation to latency since the start of treatment or the duration of use.

Secondly, no adjustment could be made in the analyses for the possible influence of confounding, because of the lack of information from individual cohort members apart from those in the sub-cohort. The comparison between the cohort sample and the general population sample showed close agreement for most of the characteristics (Table I), but the possibility of confounding might need more detailed consideration for each of the tumor sites studied. Thirdly, according to the sample survey in the cohort, progestagens were combined with estrogens in about one-third of all treatment periods. Progestagen prescriptions were not recorded, however, and could not therefore be taken into account in the analyses. Theoretically, combined treatment could either oppose or enhance the effects of estrogen exposure, as recently indicated by the finding that progestagens have different effects on the breast and the endometrium (Bergkvist *et al.*, 1989; Persson *et al.*, 1989).

Relatively little is known about the etiology of ovarian cancer. Oral contraceptives have an established protective effect, whereas the possible impact of non-contraceptive estrogens—*e.g.*, through a negative feed-back on the release of gonadotropins (Hartge *et al.*, 1988)—is still equivocal (Brinton, 1984). Case-control studies have indicated a reduced (Smith *et al.*, 1984; Hartge *et al.*, 1988), an unaltered (Annegers *et al.*, 1977; Franceschi *et al.*, 1982) and an increased (Weiss *et al.*, 1982; Cramer *et al.*, 1983) risk of developing ovarian cancer after hormone replacement therapy. In two prospective studies, the calculated rate ratios of incidence (Hunt *et al.*, 1987) and mortality (Pettiti *et al.*, 1987) were based on 6 observed cases only, which made reliable conclusions impossible. Our finding of a relative risk close to unity and a lower confidence limit of 0.74 lends no support to the recent observation of a 40% decrease in risk in women who had used menopausal estrogens (Hartge *et al.*, 1988). Future studies need to be focused specifically on the question of whether the effect of combined estrogen-progestagen treatment differs from that of estrogens alone.

Hormones may be involved in the causation of cervical cancer, but substantial confounding occurs among risk factors (Brinton, 1986; Vessey, 1986). The lack of any association in this study needs cautious interpretation. Prescription of estrogen replacement therapy is often preceded by a gynecological examination and smear-taking, followed by more frequent screening than in the background population. Such efforts entail early detection and treatment of dysplasia and *in situ* lesions and a reduced incidence of invasive cancer (Brinton, 1986; IARC, 1986). Thus, the failure to identify a substantially reduced risk of invasive cancer in this cohort may be noteworthy.

In general, the findings concerning cancer of the endometrium and breast were in accordance with those in more extensive analyses based on follow-up through 1983 (Bergkvist *et al.*, 1989; Persson *et al.*, 1989). They will therefore not be commented on further in this context. However, although the allocation to various exposure groups was probably fraught with a substantial misclassification in our study, a clear risk difference was revealed, notably for endometrial cancer, between those who received more and less potent estrogens.

According to available biological evidence and several epidemiological observations, an increased risk of developing hepato-biliary cancer would seem most likely (Williams, 1982; Bassendine, 1987). Contraceptive steroids have been associated with both benign and malignant hepatic tumors (Falk, 1982; Bosch and Muñoz, 1988). Estrogen replacement therapy may play a role in the pathogenesis of hepatic hemangiomas (Conter and Longmire, 1988). The low risk in this cohort was therefore unexpected. The magnitude of the risk decrease and the gradient in relation to the estrogenic potency (Table VI) support the validity of this new observation and point to the importance of further studies.

Our data also revealed a non-significant deficit of cancer of the pancreas. Epidemiological data on hormones and pancreatic cancer risk have been primarily indirect and equivocal (National Cancer Registry, 1987; Bourhis *et al.*, 1987; DeVesa and Silverman, 1988; Lin and Kessler, 1981; Gold *et al.*, 1985; Mack *et al.*, 1986). Colorectal cancer was seemingly unrelated to the use of estrogens in this research setting. The effect of confounding, if any, should be to bias the risk estimates upward in view of the somewhat higher educational level in the cohort than in the background population (Schottenfeld and Winawer, 1982). The evidence for a role of hormonal factors in the etiology of colorectal cancer has been weak and based mainly on indirect epidemiological observations (Brinton, 1984). Our data are more in accordance with the lack of any hormonal factors in colon cancer etiology, as found by Weiss *et al.* (1981).

Analyses of tumors of the central nervous system were included because of the recent discovery of hormone receptors at these sites, notably progesterone receptors in meningiomas, leading to hypotheses on hormonal regulation (Glick *et al.*, 1983; Moguilewsky *et al.*, 1984). Available evidence and our data, however, provide no valid basis for speculations about a causal relationship between estrogens and CNS tumors; detailed analyses by site and type proceeding from a larger number of cases will be necessary.

Some studies have suggested a relationship between steroid hormones and lung cancer (Hoover, personal communication). However, the higher prevalence of smokers in the cohort than in the background population (Table I) seems the most likely explanation for the 26% excess of lung cancers in this study.

The risk of developing renal cancer was seemingly unrelated to hormone replacement therapy (Table II). This finding conforms with that of the only previous epidemiological study addressing this issue—an odds ratio of 0.9 being found after exposure for 3 months or more to any estrogen medication (menopausal and non-menopausal estrogens, birth control pills, and diethylstilbestrol) (McLaughlin *et al.*, 1984). Diethylstilbestrol induces kidney cancer in hamsters (Kirkman and Bacon, 1950; Liehr *et al.*, 1986). Moreover, estrogens, progestin and various other hormone receptors have been demonstrated in certain human renal cancers (Vugrin, 1987), and the association between obesity and renal cancer—notably among women—in several case-control studies has suggested the role of hormonal factors (McLaughlin *et al.*, 1984; Goodman *et al.*, 1986). Nevertheless, the available epidemiological evidence does not support the idea of carcinogenic effects of non-contraceptive estrogens. In particular, the follow-up period of our cohort should be sufficiently long to make the proposed (McLaughlin *et al.*, 1984) hormonal actions during the late stages of renal carcinogenesis unlikely.

The finding of an approximately 40% excess of malignant melanoma is in agreement with a similar observation in one previous study (Holman *et al.*, 1984) of a borderline association related to the duration of use of unopposed estrogens, whereas 2 other studies found no association (Holly *et al.*, 1983; Østerlind *et al.*, 1988). Further circumstantial evidence that hormonal factors might determine the occurrence of malignant melanoma has emerged from reports on the presence of estrogen receptors in certain tumors (Fisher *et al.*, 1979; Chaudhuri *et al.*, 1980), and associations with breast cancer in some (Tucker *et al.*, 1985)—but not all (Østerlind *et al.*, 1985)—populations, and with reproductive factors (Holly *et al.*, 1983; Gallagher *et al.*, 1985). More direct epidemiological

support comes from the finding of a decreased risk of developing skin melanomas after bilateral oophorectomy (Gallagher *et al.*, 1985) and after treatment with irradiation for cervical cancer (but not among non-irradiated women with this disease), which might entail ovarian ablation (Storm, 1988). Our own data give limited support to this hypothesis. The role of chance and possible confounding by sun exposure (Elwood *et al.*, 1985) must be considered, particularly in view of the lack of a biological gradient in the subgroup analyses.

We conclude that this prospective study has provided generally reassuring results concerning possible carcinogenic effects of hormone replacement therapy outside of endometrial and breast cancer. However, one potentially important constraint of this analysis relates to the duration of follow-up. The mean observation time from the first prescription recording was 6.7 years, but the sub-cohort survey showed that many women had been exposed for several years before inclusion in the cohort. Although assumed carcinogenic effects on the breast and notably on the endometrium will have already occurred in the cohort, the latency period might still be too short to exclude tumor induction in other organs, particularly if estrogens affect early events in the multi-step carcinogenic process.

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